REVIEW ARTICLE

# Histopathology as a Diagnosis Tool of Abdominal Tuberculosis: A Narrative Review of Evidence

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## Abstract

**Background and aim:** Abdominal tuberculosis (ATB) poses significant diagnostic challenges due to its varied clinical manifestations and its ability to mimic other diseases. Histopathology is a promising diagnostic tool to diagnose ATB. This narrative review aims to synthesize evidence on the evolving role of histopathology in diagnosing ATB, highlighting its integration with molecular and microbiological diagnostics, and discussing its limitations and emerging technologies.

**Methodology:** A structured search of databases including PubMed, Scopus, Web of Science, and Google Scholar was performed, focusing on literature published from January 2002. The review includes peer-reviewed original articles on the diagnosis of ATB using histopathology and integrated diagnostic modalities.

**Results:** Histopathology remains crucial for diagnosing ATB, especially in resource-limited settings, due to its ability to visualize granulomatous inflammation and other cellular features. The integration of histopathology with molecular diagnostics like GeneXpert *Mycobacterium tuberculosis*/rifampicin (MTB/RIF) and tuberculosis polymerase chain reaction (TB-PCR) has improved diagnostic accuracy. However, limitations include diagnostic overlap with other conditions and the impact of prior treatment on tissue samples. Emerging technologies such as digital pathology and artificial intelligence (AI)-driven image analysis are poised to enhance diagnostic precision.

**Conclusion:** The review underscores the importance of a multimodal diagnostic approach, combining histopathology with other techniques to improve sensitivity and specificity. As ATB continues to be a global health concern, advancements in histopathological techniques and interdisciplinary collaboration are essential for timely and accurate diagnosis.


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## Introduction

Abdominal tuberculosis (ATB), a manifestation within the spectrum of extrapulmonary tuberculosis (EPTB), remains a particularly challenging entity to diagnose owing to its protean clinical presentations, low bacillary load, and frequent imitation of other chronic granulomatous or neoplastic disorders, including Crohn's disease, sarcoidosis, and various intraabdominal malignancies.[1] While the global incidence of pulmonary tuberculosis has shown a gradual decline in certain regions, the prevalence of extrapulmonary disease, particularly ATB, has remained static or even escalated in vulnerable populations such as those with HIV coinfection, malnutrition, or other causes of immune compromise.[2]

Diagnosis is often delayed due to the insidious onset of symptoms, vague constitutional complaints, and the poor sensitivity of conventional microbiological assays in paucibacillary disease.[3] Radiologic evaluation, though valuable, frequently yields nonspecific findings with significant overlap across other inflammatory or neoplastic abdominal pathologies. Molecular assays such as GeneXpert *Mycobacterium tuberculosis*/rifampicin (MTB/RIF) and tuberculosis polymerase chain reaction (TB-PCR) have improved specificity and shortened turnaround times; however, their performance remains inconsistent, particularly when applied to formalin-fixed paraffin-embedded (FFPE) material.[4] For this reason, histopathological examination of biopsy tissue continues to be a cornerstone in the diagnostic algorithm, especially in low-resource environments where advanced molecular platforms may be inaccessible.[3,5]

Histopathology permits direct visualization of the morphological hallmarks of tuberculous inflammation, including granulomas composed of epithelioid histiocytes, Langhans-type giant cells, and variable degrees of central caseous necrosis.[6] Although these changes are characteristic, they are not pathognomonic, necessitating integration with clinical, radiologic, and microbiologic data to establish a definitive diagnosis. In recent years, the histopathologist's role has expanded from pure morphological interpretation to the use of adjunctive techniques such as immunohistochemistry (IHC) and molecular-based detection methods, which together have enhanced diagnostic precision.[7,8]

This review synthesizes literature published from January 2002, exploring the evolving histopathological approach to ATB, its interface with ancillary diagnostic modalities, and its clinical application in both high- and low-burden settings (Table 1). Special attention is directed toward advances in tissue processing, recognition of interpretative pitfalls, and the integration of novel technologies, aimed at equipping both clinicians and diagnostic pathologists with a refined, practical framework for accurate and timely ATB diagnosis.

## Methodology

### Study Design and Objective

This article is a narrative review aiming to synthesize the evolving role of histopathology in the diagnosis of ATB.

### Primary Objective

To evaluate advancements in histopathological techniques, their integration with molecular and microbiological diagnostics, and their clinical implications in both endemic and nonendemic settings.

### Focused Research Questions

- What are the histopathological features of ATB across various organ systems?
- How has the diagnostic role of histopathology evolved over the last two decades in the context of ATB?
- What is the diagnostic utility of combining histopathology with adjunctive tests such as Ziehl–Neelsen (ZN) staining, GeneXpert MTB/RIF, TB-PCR, culture, and IHC?

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**Table 1:** Characteristic description of the diagnostic modalities for ATB

| *Diagnostic modality* | *Principle* | *Strengths* | *Limitations* | *Best used when* |
|---|---|---|---|---|
| Histopathology (H&E stain) | Morphological visualization of granulomas and necrosis | Widely available, high specificity for classical lesions | Cannot confirm etiology alone; limited in early/treated cases | Granulomatous inflammation suspected |
| ZN stain | Detects AFB in tissue | Specific for mycobacteria if positive | Very low sensitivity (10–40%) | Necrotizing granulomas present or suspected |
| GeneXpert MTB/RIF | PCR-based detection of MTB DNA and rifampicin resistance | Rapid, detects resistance, good specificity | Moderate sensitivity in FFPE tissue | Need for rapid confirmation or drug resistance profiling |
| Mycobacterial culture (MGIT/LJ) | Grows live bacilli from biopsy or fluid | Gold standard for confirmation; drug susceptibility testing | Time-consuming (up to 8 weeks), requires viable bacilli | Definitive confirmation and drug resistance assessment needed |
| IHC (e.g., MPT64, VP-M660) | Detection of MTB antigens in tissue | Enhances specificity when granulomas are ambiguous | Limited availability; antibody variability | Differentiating TB from Crohn's or other granulomatous diseases |
| Radiological imaging (CT/MRI) | Identifies patterns of lymphadenopathy, thickening, ascites | Noninvasive, guides biopsy sites | Nonspecific, unable to differentiate TB from malignancy alone | Planning biopsy or evaluating disease extent |

- What are the diagnostic limitations associated with histopathological interpretation in ATB?
- What emerging technologies are influencing the future role of histopathology in ATB diagnosis?

### Eligibility Criteria for Literature

The selection of literature for this review was based on the following criteria:

- Inclusion: Peer-reviewed original articles published from January 2002 focusing on the diagnosis of ATB using histopathology and/or integrated diagnostic modalities.
- Exclusion: Non-English articles, case series, animal studies, editorials, conference abstracts without full text, and studies unrelated to ATB or histopathology were excluded.

### Search Strategy and Sources

A structured search of the following databases was performed—PubMed, Scopus, Web of Science, and Google Scholar. The search included combinations of the following Medical Subject Headings (MeSH) and keywords:

- "Abdominal tuberculosis,"
- "Histopathology,"
- "Granulomatous inflammation,"
- "Ziehl–Neelsen stain,"
- "GeneXpert MTB/RIF,"
- "TB-PCR,"
- "Immunohistochemistry,"
- "MPT64,"
- "VP-M660,"
- "Diagnostic accuracy," and
- "Digital pathology in tuberculosis."

Manual screening of the reference lists of relevant articles and review papers was also conducted to identify additional eligible studies.

### Data Synthesis and Presentation

This review follows a narrative synthesis approach, organizing the evidence under the clinical landscape, histopathological evolution, combinatorial diagnostics, limitations, and emerging technologies. Findings were qualitatively integrated without formal meta-analysis due to heterogeneity in study designs, histological criteria, and diagnostic protocols.

## Pathophysiological and Clinical Landscape

Abdominal tuberculosis encompasses a diverse range of anatomical and pathological presentations, typically categorized into peritoneal, lymph nodal, luminal (involving the small and large intestine, gastroduodenum, and esophagus), and solid-organ disease affecting the liver and spleen.[9] While each subtype exhibits distinct pathological traits, they share a unifying basis of chronic granulomatous inflammation driven by cell-mediated immunity and delayed-type hypersensitivity.[10]

The histopathological signature of ATB is the granuloma comprising epithelioid histiocytes, Langhans-type multinucleated giant cells, and a surrounding lymphocytic mantle.[11] Although the presence of caseous necrosis strongly favors a tuberculous etiology, it is not invariably present, particularly in immunosuppressed patients.[3] In peritoneal involvement, the serosal surfaces often demonstrate diffuse thickening studded with submesothelial granulomas, which can closely mimic peritoneal carcinomatosis.[12] Nodal disease typically presents as enlarged, matted lymph nodes with central necrosis and fibrosis.[13] Intestinal tuberculosis (ITB) most frequently affects the ileocecal region, producing transmural inflammation, ulceration, and fibrotic strictures—findings that overlap considerably with Crohn's disease.[14]

From a clinical perspective, ATB often escapes early recognition. Symptoms tend to be vague and nonspecific, including abdominal discomfort, low-grade fever, anorexia, altered bowel habits, and routine laboratory parameters may offer little specificity. Consequently, a pivotal role is retained by the histopathological chapter, particularly where clinical and radiological findings are aligned and streamlined with primary diagnosis.

## Evolution of Histopathology in Abdominal Tuberculosis Diagnosis

Over the past two decades, histopathology's contribution to ATB diagnosis has evolved from reliance on morphological pattern recognition to a multidimensional discipline incorporating IHC, ancillary staining, and, increasingly, digital image analysis (Fig. 1).

Hematoxylin and eosin (H&E) staining remains the bedrock, enabling recognition of granulomatous inflammation and necrosis.[15] However, due to significant histological overlap with other granulomatous conditions, additional stains such as ZN for acid-fast bacilli (AFB) have long been employed.[16] Unfortunately, paucibacillary lesions often yield negative ZN results, limiting sensitivity.[17] Publications from the early 2000s consistently highlighted this limitation and advocated a multimodal interpretive strategy.[18–22]

Immunohistochemistry markers, particularly MPT64, have substantially improved the ability to distinguish tuberculous

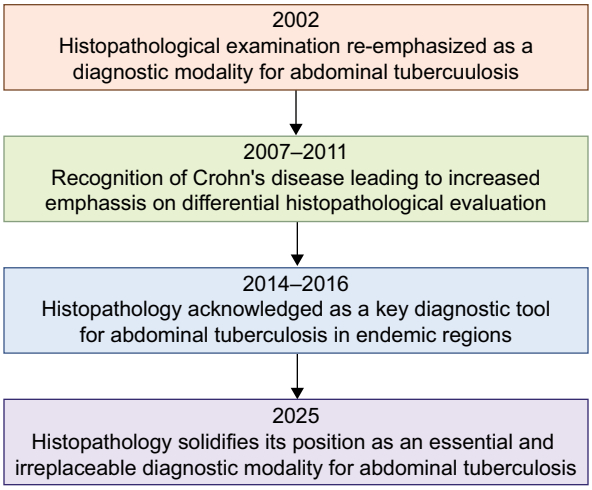


**Fig. 1:** Evolution trajectory of histopathology for ATB diagnosis[15–18]

from nontuberculous granulomatous inflammation.[23] More recently, advanced immunostains targeting TB-specific antigens such as VP-M660 have been introduced, with studies from 2010 onwards validating their value in endemic regions where Crohn's disease and ATB share marked histological similarity.[24,25] Advances have also occurred in tissue handling, fixation, and granuloma classification, with semiquantitative scoring of necrosis and lesion distribution now under active exploration for standardized reporting.

## Combinatorial Diagnostic Approaches

Although histopathology remains central to diagnosis, its yield is greatly enhanced by integrating it with molecular, microbiological, and imaging modalities. The modern paradigm favors composite diagnostics in which histological impressions are reinforced by confirmatory laboratory data.[26]

Molecular assays such as the GeneXpert MTB/RIF have gained traction, demonstrating high specificity in detecting *M. tuberculosis* deoxyribonucleic acid (DNA) and rifampicin resistance even in FFPE samples.[27,28] Studies conducted between 2012 and 2020 indicate that coupling GeneXpert with histopathology can raise diagnostic sensitivity by 15–20% without loss of specificity.[29–32] TB-PCR, while more variable due to differences in amplification targets and protocols, offers particular utility in paucibacillary specimens.[33]

Culture techniques such as Mycobacterial Growth Indicator Tube (MGIT) and Lowenstein–Jensen media remain the microbiological reference standards, albeit with longer turnaround times.[34] Used alongside histology, they permit both morphological correlation and microbiological confirmation. IHC bridges the gap between these approaches by identifying mycobacterial antigens directly within granulomatous foci.[35] As of 2025, an optimized diagnostic pathway commonly involves a layered combination of H&E, ZN stain, IHC, and nucleic acid amplification testing.[36]

## Discussion

Abdominal tuberculosis continues to pose a web of diagnostic challenges, owing to its complexity of clinical manifestations, overlapping radiological findings, and histopathological convergence with other granulomatous entities. The Langhans-based giant cells and caseation necrosis remain a morphological cornerstone, despite the epithelioid granulomas.[6,18] These features are often variably expressed and frequently entangled with immunocompromised hosts or hosts preexposed to empirical antitubercular therapy. The distinction from mimics such as Crohn's disease and sarcoidosis is further obfuscated by the occurrence of noncaseating granulomas, necessitating careful synthesis of histomorphology with ancillary investigations.[3]

Histopathology, long considered the diagnostic bedrock for ATB, has undergone a substantive evolution over the last two decades. The interpretive framework has shifted from reliance solely on morphological pattern recognition to a composite, multimodal strategy in which routine H&E sections are complemented by ZN staining, IHC, and, increasingly, nucleic acid amplification assays. In this integrative paradigm, IHC markers such as MPT64 and VP-M660 have shown appreciable discriminatory value in differentiating tuberculous from nontuberculous granulomatous inflammation, especially in high-burden settings where clinical and histological overlap is commonplace. When molecular platforms such as GeneXpert MTB/RIF are codeployed with histopathology, incremental gains in sensitivity have been documented without erosion of specificity, particularly in paucibacillary lesions.

### Limitations and Diagnostic Pitfalls

Despite its value, histopathology in ATB diagnosis faces inherent constraints. Noncaseating granulomas may be indistinguishable from those of Crohn's disease, sarcoidosis, or certain fungal infections in the absence of necrosis or demonstrable AFB.[37] Morphology can also be distorted by prior empirical therapy, inadequate sampling, or immunosuppression.

Interobserver variability, particularly in low-incidence regions or resource-limited settings, may reduce consistency. The absence of universally accepted histological criteria for ATB complicates reproducibility. ZN staining, though highly specific, remains insensitive for lesions with low bacillary burden. Negative staining should therefore not exclude TB when other morphological and clinical pointers are present.

Technical factors, such as suboptimal fixation, delayed processing, or insufficient sampling, can further degrade diagnostic quality. Vigilance in specimen handling and adherence to robust processing protocols are essential for preserving histological integrity.

### Emerging Trends and Technologies

Recent advances are reshaping histopathology's diagnostic reach. Digital pathology, advances in regenerative medicine, and artificial intelligence (AI)-assisted image analysis promise more standardized interpretations and potentially higher sensitivity in detecting subtle granulomatous changes.[38,39] Machine-learning models are now capable of quantifying necrosis, identifying granuloma subtypes, and flagging morphological nuances invisible to routine light microscopy.

Novel multiplex IHC and mRNA *in situ* hybridization techniques offer concurrent morphological and molecular insights from a single tissue section.[40] RNA-based probes for *M. tuberculosis* transcripts have shown promising yield in recent studies, particularly when DNA quality is compromised in archival specimens.[41,42] Whole-slide imaging and cloud-based consultation platforms are expanding access to subspecialist expertise, a particular advantage in settings where infectious-disease pathologists are scarce.

## Conclusion

Histopathology continues to serve as a cornerstone in ATB diagnosis, its utility amplified when combined with molecular and microbiological tools. Recent advances in IHC,

nucleic acid amplification tests (NAATs), and digital pathology are enhancing both sensitivity and specificity, even in diagnostically complex cases. While limitations persist, ongoing refinement in sampling, processing, and interpretive technologies is steadily narrowing these gaps. Future integration of AI-assisted diagnostics, harmonized histological criteria, and global collaborative platforms could transform ATB histopathology into a more precise, reproducible, and high-throughput discipline. In high-burden settings, the path forward lies in sustained interdisciplinary collaboration, ensuring timely and accurate diagnosis for optimal patient outcomes.

## Orcid

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